Studies have been conducted to compare conventional in vivo genotoxicity tests (e.g., the cytogenetic assay in bone marrow or peripheral blood) with these animal models. It appears that data collected from transgenic animals, in these cases, are more relevant to an assessment of possible risk in man (141).

Another application of transgenic animals in safety assessment is the evaluation of drugs derived from biological molecules such as interferons and recombinant immunoglobulins. Because of the nature of these molecules, the host immune response-mediated pathogenicity is the primary concern when they are to be used for therapeutic purposes. In this case, transgenic animals are made to express these biological molecules for a comparison to normal animals in order to assess the immunopathogenic responses (142,143).

4. THE PROSPECTIVE

4.1. Technical Development

The basic tools to mutate a mouse genome, such as pronuclear DNA injection, blastocyst injection, and vectors for gene targeting, are all well established. Two potentially problematic aspects of this technology stem from the following facts: it is very time consuming to establish targeted ES clones and generate chimeric mice, and useful ES cells are available only from the mouse and the rat. For the first problem, the aggregation method to introduce ES cells into embryos provides an alternative; however, this procedure requires fine tuning. Recent development in generating ES banks representing a large number of gene-targeting clones can potentially shorten the time required for ES work (144). However, the remaining challenge is the connection of each targeted gene to a special disease condition, which requires enormous amounts of basic research. In order to address the second problem, it is necessary to establish ES cells from a variety of animal species that are capable of colonizing gonads efficiently. This problem also requires an enormous amount of effort in research to understand the mechanisms underlying germ cell development.

The design of experimental procedures that allow different genetic tools to be used in combination can also be improved. For instance, the combined use of two transgenic systems, one with the *Cre* gene under the control of a specific promoter and the other with targeted delivery of the *loxP* sites, allows various types of specific gene alterations to be constructed in animals. The level of specificity and the magnitude of alteration can be improved tremendously by careful design. A critical factor is the identification of tissue- and cell-specific regulatory elements for a wide variety of conditions. This essential piece of information awaits more effort in basic biological research. Finally, one should not ignore the complexity of